REMARKS

Applicants appreciate the examination evidenced by the Final Official Action ("Final Action") mailed August 5, 2002. In response, Applicants have filed the accompanying Request for Continued Examination with this Amendment which Applicants respectfully request the entry of prior to the examination of the present claims.

Applicants have amended Claims 12-15, 19, and 21 to further clarify the subject matter of the present invention. Support for amended Claims 12-15, 19, and 21 can be found in the specification at page 6, lines 19-24 and page 10, lines 15-22. Applicants have added new Claim 26, support for which can be found at page 10, lines 23-29.

Applicants have amended Claims 12-15 and 21 to delete the now superfluous recitation "endothelial-inhibiting amount" and to identify a preferred embodiment of the antineoplastic chemotherapeutic agent as "cisplatin." Moreover, Claim 12 has been amended to recite that "erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of said cisplatin." Claim 19 has been amended to merely correct claim dependency in view of the cancellation of Claim 17 (along with Claims 18 and 22) without prejudice or disclaimer. Applicants have also added Claim 26 that recites, among other things, that "cisplatin is administered in a manner selected from the group consisting of intravenous, intramuscular, intraperitoneal, subcutaneous, intratumor, and intrapleural injection. " In view of the further clarification of the claims as presented in the current Amendment, Applicants respectfully submit that Claims 12-15, 17-25, and newly added Claim 26 are enabled under 35 U.S.C. § 112, first paragraph, are not anticipated under 35 U.S.C. § 102, and are nonobvious under 35 U.S.C. § 103 as discussed herein below in greater detail.

I. Claims 12-15, 17-25, and New Claim 26 Are Enabled Under 35 U.S.C. § 112, First Paragraph

Claims 12-15, 17-25, and new Claim 26 are enabled under 35 U.S.C. § 112, first paragraph. The Court of Appeals for the Federal Circuit has articulated the test of enablement in terms of "whether one skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." United States v. Telectronics, Inc., 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). Contrary to the assertions of the Final Action, the specification provides enablement for a method of treating a solid vascularized tumor with cisplatin in combination with erythropoietin. In view of the level of skill of those in the art, the disclosure provided in the present application (*see* specifically, page 12, line 26 through page 18, line 15 which includes examples), and the common practice of developing treatment protocols to suit the needs of the specific patient, Applicants submit that one skilled in the art pertinent to this invention would not be forced to exercise undue experimentation in order to determine which mode (i.e., dosage and treatment protocol) of administration would be most appropriate for treating a solid vascularized tumor.

To support the enablement rejection under 35 U.S.C. § 112, first paragraph, the Final Action further relies on the Rule 132 Declaration of Dr. Anagnostou ("the Anagnostou Declaration") submitted to the U.S.P.T.O. in reference to related application serial number 08/842,700, now issued U.S. Patent No. 5,922,674. Applicants direct the Examiner's attention to the later submitted Rule 132 Declaration of Dr. George Sigounas ("the Sigounas Declaration"). A copy is enclosed for the Examiner's reference.

The Sigounas Declaration presents *in vivo* data from experiments designed to assess the ability of erythropoietin delivered concomitantly with a chemotherapeutic agent, such as cisplatin, to inhibit endothelial cell proliferation in tumors, and thus inhibit tumor vascularization and suppress tumor growth. The data set forth in the Sigounas Declaration evaluating tumor neovascularization, reduction in tumor mass, reduction in tumor volume, and histological analysis of tumor sections confirms enablement for methods of treating a

solid vascularized tumor in a subject in need of such treatment wherein the method comprises administering cisplatin in conjunction with erythropoietin, wherein the erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of cisplatin as recited in amended Claim 12. Moreover, the data provided in the Sigounas Declaration coupled with the knowledge possessed by those of ordinary skill in the art and the disclosure in the present application, both as discussed above, demonstrates enablement for methods of treating a solid vascularized tumor, comprising among other things, administering cisplatin in conjunction with erythropoietin, wherein erythropoietin is administered in an amount of from about 750 Units per kilogram to about 2,000 Units per kilogram as recited in amended Claim 21. Thus, Claims 12-15, 17-25, and new Claim 26 are enabled under 35 U.S.C. § 112, first paragraph.

Accordingly, Applicants respectfully submit that Claims 12-15, 17-25, and new Claim 26 are enabled under 35 U.S.C. § 112, first paragraph, and request that this rejection be withdrawn.

II. Claims 12-15, 17-25, and New Claim 26 Are Patentable Under 35 U.S.C. § 102 Over Platanias et al.

Claims 12-15, 17-25, and new Claim 26 are patentable under 35 U.S.C. § 102 over Platanias et al., *J. Clin. Oncol*, 9:2021-2026 (1991) (Platanias). Applicants note that a finding of anticipation further requires that there must be no difference between the claimed invention and the disclosure of the cited reference as viewed by one of ordinary skill in the art. *See Scripps Clinic & Research Foundation v. Genentech Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991).

The present invention relates to **treatment of solid vascularized tumors** comprising, among other things, administering cisplatin in conjunction with erythropoietin, wherein said erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of said cisplatin as recited in Claim 12. It is important to note that, as stated in the present application at page 5, lines 7-9, tumors require an

adequate blood supply, and growth of new vessels in the tumor mass is stimulated by angiogenic factors secreted by tumor tissue. In contrast, Platanias et al. merely proposes a **treatment of chemotherapy-induced anemia**. Therefore, Platanias et al. does not disclose each and every recitation of the claimed invention directed to methods of treating a **solid vascularized tumor** in a subject in need of such treatment, **comprising administering cisplatin in conjunction with erythropoietin, wherein erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of said cisplatin** as recited in amended Claim 12.

Moreover, the method proposed by Platanias et al. would not inherently treat a solid vascularized tumor. As noted in the specification at page 4, lines 29 through page 5, line 5, the present inventors have found that erythropoietin can effectively prevent and/or repair endothelial damage caused by chemotherapeutic agents. The present inventors have also found that administration of erythropoietin concomitantly with chemotherapeutic agents produces a biphasic response: certain doses of erythropoietin protect endothelial cells from the deleterious effects of the chemotherapeutic agent, while increased doses enhance the endothelial growth-suppression caused by the chemotherapeutic agent. Thus, it is only in view of the disclosure of the present invention is one of ordinary skill in the art provided guidance to arrive at methods of treating a solid vascularized tumor in a subject in need of such treatment, comprising administering cisplatin in conjunction with erythropoietin, wherein **erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of cisplatin** as recited in amended Claim 12. Amended Claim 21 further recites a method of treating a solid vascularized tumor comprising, among other things, administering cisplatin in conjunction with erythropoietin wherein erythropoietin is administered in an amount of from about 750 Units per kilogram to about 2,000 Units per kilogram. Platanias et al. does not disclose methods of treating solid vascularized tumors as recited in amended Claim 21. Thus, Claims 12-15, 17-25, and new Claim 26 are patentable over Platanias et al.

Accordingly, Applicants respectfully submit that Claims 12-15, 17-25, and new Claim

26 are not unpatentable under 35 U.S.C. § 102 in view of Platanias et al. and request that this rejection be withdrawn.

III. Claims 12-15, 17-25, and New Claim 26 Are Not Unpatentable Under 35 U.S.C. § 103 In View of the Cited References

Claims 12-15, 17-25, and new Claim 26 are not unpatentable under 35 U.S.C. § 103 over Platanias et al. and further in view of Markham et al., *Drugs*, 49:232-254 (1995) and also Wood et al., *J. Clin. Invest.* 95: 1650-1659 (1995). In contrast to the assertions of the Final Action, the cited references either alone, or in combination, fail to suggest all the claim recitations of the present invention. The cited references, in some form, relate to treating chemotherapy-induced anemia. The cited references, alone or in combination, do not teach or suggest methods of treating a solid vascularized tumor in a subject in need of such treatment, comprising administering cisplatin in conjunction with erythropoietin, wherein erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of cisplatin as recited in amended Claim 12.

As stated above, tumors require an adequate blood supply and growth of new vessels in the tumor mass is stimulated by angiogenic factors secreted by tumor tissue. The present inventors have shown the use of erythropoietin to enhance endothelial growth-suppression during chemotherapy as being useful in treating, among other things, angiogenic tumors, where it is desirable to prevent or slow the formation of new blood vessels which support tumor growth. The cited references, even if combined, merely propose a method of treating chemotherapy-induced anemia and **do not** teach or suggest a method of treating a solid vascularized tumor as recited in the amended Claims 12 and 21. Thus, Claims 12-15, 17-25, and new Claim 26 are patentable over the cited references, and Applicants respectfully request that this rejection be withdrawn.

Accordingly, Applicants submit that Claims 12-15, 17-25, and new Claim 26 are enabled under 35 U.S.C. § 112, are not anticipated under 35 U.S.C. § 102, and are nonobvious under 35 U.S.C. § 103, and thus, respectfully request allowance of all claims.

Conclusion

In view of the foregoing remarks, Applicants respectfully request allowance of all claims in due course and that a Notice of Allowance be issued in due course. Any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on February 3, 2003.

Vickie Diane Prior
Date of Signature: February 3, 2003

Version With Markings To Show Changes Made

In the Claims:

Please amend Claim 12 as follows:

12. (Amended) A method of treating a solid vascularized tumor in a subject in need of such treatment, comprising administering cisplatin **[an antineoplastic chemotherapeutic agent]** in conjunction with **[an endothelial-inhibiting amount of]** erythropoietin, wherein said erythropoietin is administered in an amount effective to enhance suppression of endothelial growth associated with administration of said antineoplastic chemotherapeutic agent.

Please amend Claim 13 as follows:

13. (Amended) A method according to claim 12, wherein said **[endothelial-inhibiting amount of]** erythropoietin is administered concurrently **[simultaneously]** with said cisplatin **[chemotherapeutic agent]**.

Please amend Claim 14 as follows:

14. (Amended) A method according to claim 12, wherein said **[endothelial-inhibiting amount of]** erythropoietin is administered prior to said cisplatin **[chemotherapeutic agent]**.

Please amend Claim 15 as follows:

15. (Amended) A method according to claim 12, wherein said **[endothelial-inhibiting amount of]** erythropoietin is administered after said cisplatin **[chemotherapeutic agent]**.

Please amend Claim 19 as follows:

19. (Amended) A method according to claim 12 **[17]**, wherein said cisplatin is administered intravenously.

Please amend Claim 21 as follows:

21. (Amended) A method of treating a solid vascularized tumor in a subject in need of such treatment, comprising administering cisplatin **[an antineoplastic chemotherapeutic agent]** in conjunction with **[an endothelial-inhibiting amount of]** erythropoietin;

wherein said erythropoietin is administered in an amount of from about 750 Units per kilogram to about 2,000 Units per kilogram.